The Successful Pharmacological Treatment of Adolescents and Young Adults with Borderline Personality Disorder: A Preliminary Open Trial of Flupenthixol

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Borderline personality disorder is a significantly disabling disturbance often arising in adolescents or young adults. In the absence of demonstrated effective treatments in this population, this open prospective study evaluated the effect of low dose (3 mg per day) flupenthixol in 13 rigorously diagnosed adolescents with borderline personality disorder. Therapeutic outcome over eight weeks of treatment assessed across measures of impulsivity, depression/dysphoria, general psychopathology and global functioning showed significant improvement in all spheres. These findings suggest that low dose flupenthixol may have a role to play in the short-term treatment of this population.

Key Words: borderline personality disorder, adolescents, flupenthixol

INTRODUCTION

Borderline personality disorder (BPD) is a serious personality disturbance that often onsets in the adolescent years and has not been shown to be effectively or efficiently treated by psychosocial interventions (Kutcher and Korenblum 1992; Egan 1988; Shay 1987). BPD may be a lifelong disturbance that interferes with an individual's functioning in social, interpersonal, family or academic/vocational areas. BPD has a high morbidity and increased mortality and may be found concurrently with depressive symptoms and substance abuse. It also overlaps with other psychiatric disturbances including mood and eating disorders and, possibly, post-traumatic stress disorder (Stone et al 1987; Marton et al 1989; McManus et al 1984; Gunderson and Zanarini 1987; Traskman-Bendz et al 1986; Akiskal et al 1983; Dulit et al 1990).

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Despite a lack of evidence for therapeutic efficacy, adolescents suffering from BPD are commonly treated with a variety of psychosocial therapies. For example, a study of the clinical approach to a teenager with BPD conducted in a cohort of Canadian child and adolescent psychiatrists showed that the preferred interventions were individual or family therapies (Kutcher and Korenblum 1992). The therapeutic literature regarding this disorder often argues for long-term inpatient or residential care. However, no valid evidence exists to show that any of these treatment modalities are at all effective in either ameliorating the core symptoms or decreasing the functional morbidity of teens with BPD. The direct costs of these treatments, however, are considerable (Kutcher and Korenblum 1992).

Neurobiological studies of adolescents with BPD are not yet available. However, investigations of adults with BPD have suggested that the affective and behavioral dysregulations found in BPD may be associated with both dopamine and serotonergic neurotransmitter system dysfunction in

Table 1

Subjects undergoing flupenthixol treatment

Sex	Female	11
	Male	2
Age	Range	14 - 22
	Mean	17.2
Previous hospitalizations	0	5
	1 - 2	5
	>3	3
Previous self-mutilation incidents	0	1
	1 - 2	2
	3 - 5	2
	>5	8
Previous suicide attempts	0	3
	1 - 2	6
	3 - 5	2
	>5	2
History of alcohol use	None	5
	Mild	3
	Significant	5
History of substance use	None	7
	Mild	1
	Significant	5
Previous treatments	Psychotherapy	12
	Anti-depressants	7
	Lithium	3
	Neuroleptics	5
	Anxiolytics	5

many patients. For example, individuals with BPD show abnormal responses to minor stressors — a behavioral phenomenon possibly modulated by mesocortical dopamine systems (Glowinski et al 1984). Biological markers possibly associated with central nervous system dopaminergic functioning have been found to be abnormal in many adults with BPD. These markers include disordered smooth pursuit eye tracking and prolonged long latency auditory evoked potentials — the P300 (Siever et al 1986; Kutcher et al 1987; Lahmeyer et al 1989). Further, patients with BPD have been described as showing dysphoric responses to dopaminergic compounds (Lucas et al 1987; Schulz et al 1985). Additionally, some patients with BPD show abnormal neuroendocrine responses to serotonergic system pharmacologic stimulation (Traskman-Bendz et al 1986; Coccaro et al 1989; Coccaro et al 1990; Siever et al 1992; Lahmeyer et al 1989). Consistent with this hypothesis are reports in the literature on adults showing successful short-term pharmacologic treatment of BPD symptoms with low dose neuroleptics as compared to unconvincing or negative outcomes with tricyclic antidepressants, thymoleptics or anxiolytics (Kutcher and Blackwood 1989; Links and Steiner 1988; Soloff et al 1986; Leone 1982; Cole et al 1984; Serban and Seigel 1984; Goldberg et al 1986; Gardner and Cowdry 1989; Gardner and Cowdry 1986; Cowdry and Gardner 1988; Soloff 1989; Soloff 1990).

Consideration of both biologic and psychopharmacologic findings in adults with BPD led to the consideration of using flupenthixol, a neuroleptic of the thioxanthene group, in the short-term treatment of adolescents with BPD. Only one previous pharmacologic study — an open trial using mesoridazine (45 mg per day) in a diagnostically heterogeneous group of personality disordered adolescents — has, as far as is known, been reported (Barnes 1977). Difficulties with the study design, however, preclude any clear-cut determination of the potential value of neuroleptic type medications in the BPD population. Flupenthixol in low doses (Gruber and Cole 1991; Montgomery and Montgomery 1984) was chosen for evaluation for the following reasons: 1. its proven dopaminergic (D_1 and D_2 receptor effects) antipsychotic activity; 2. its potential antidepressant and antidysphoric efficacy (serotonin-receptor 5-HT_2 mediated); and 3. its demonstrated good tolerability in the psychotic disorders clinic in terms of generally mild to moderate extrapyramidal side-effects in teenagers treated (albeit at higher doses) for psychotic disorders.

Because adolescents demonstrate different psychological, social and biologic features from adults (they are not simply adults — just younger) psychopharmacologic treatments must be scientifically evaluated as to efficacy, tolerability and safety in this population and not extrapolated from psychopharmacologic studies of adults. For example, tricyclic antidepressants, although of demonstrated therapeutic efficacy in adult depressives, have not been shown to be more effective than placebo in treating depressed adolescents (Ryan 1990; Kutcher et al 1994). Thus, based on the suggested evidence from literature on adults and the clinical observations of the authors (outlined above) it was hypothesised that low dose flupenthixol (3 mg per day) may decrease impulsivity and dysphoria, and improve psychiatric morbidity in adolescents with borderline personality disorder. As this is the first study of its kind in this population, an open trial design was chosen to ensure that all reasonable precautions concerning the use of this medication would be taken. A positive result in this open trial was identified as a necessary first step toward further evaluation using a double-blind placebo controlled design.

METHOD

Subjects and Diagnosis

Subjects were recruited from the adolescent group home population of two youth agencies specializing in community interventions with emotionally disturbed teens in a large urban area. After approval for agency participation had been

given by an administrator from each agency, the authors met with agency staff to describe the study, review inclusion and exclusion criteria, and present an update on adolescent borderline personality disorder. Subjects were referred to the study by group home personnel. The study took place in the outpatient clinic area of an adolescent psychiatric treatment program located in a university teaching hospital.

Thirteen consecutively diagnosed adolescents and young adults (two male, 11 female) aged 14 to 22 years (mean age 17.2 years) who met DSM-III-R criteria for BPD as defined by clinical interview and had a score of ≥ 7 on the Diagnostic Interview for Borderlines (DIB) (Gunderson et al 1981; Yanchyshyn et al 1986) entered the study. In addition to the evaluations noted above, each teenager was further assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers et al 1985) and the Hyler Personality Inventory. After giving informed consent and undergoing a baseline medical evaluation, students entered the study only if they met both DSM-III-R criteria and DIB for BPD in the absence of any concurrent Axis I disorder (see Table 1).

Symptomatic assessments

Subjects were assessed at baseline and at two week intervals for eight consecutive weeks using the following instruments:

Observer-rated: Global Assessment Scale (GAS) (Psychopharmacology Bulletin 1985), Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), Ward Scale of Impulsivity (WSI) (Soloff et al 1986), Brief Psychiatric Rating Scale (BPRS), (Overall and Gorham 1962), Life Stressors Subscale of the WSI (LS-WSI) (Soloff et al 1986), Abnormal Involuntary Movements Scale (AIMS) (Lane et al 1985).

Self-rated: Beck Depression Inventory (BDI) (Beck et al 1961), Symptom Check List - 58 (SCL-58) (Derogatis et al 1974).

Subjects were financially compensated for time and travel costs involved in study participation.

Treatment

After giving informed consent, subjects were treated with flupenthixol using the following titration schedule: 1 mg once per day for three consecutive days followed by 2 mg once per day for three consecutive days followed by 3 mg once per day for the study duration. In addition, subjects were treated with procyclidine hydrochloride (5 mg to 10 mg per day) to provide prophylactic control of potential extrapyramidal side-effects. Administration of medication was supervised by a responsible adult. Pre- and post-levels of symptom ratings were analysed using the student t-test.

Table 2

Outcome measures in multiple domains in 13 adolescents/young adults treated with flupenthixol

Measure	Mean value pre-treatment	Mean value post-treatment	Significance
Ward Scale of Impulsivity	14.4	6.9	$p = 0.001$
Beck Depression Inventory	26.9	17.3	$p = 0.02$
Hamilton Depression Rating Scale	13.6	9.3	$p = 0.03$
Symptom Checklist 58	129.6	99.0	$p = 0.006$
Brief Psychiatric Rating Scale	13.5	7.6	$p = 0.01$
Global Assessment Scale	36.6	48.6	$p = 0.004$
Life Stressors Subscale of the Ward Scale of Impulsivity	7.0	5.7	$p = 0.281$

RESULTS

Eleven of the 13 patients completed the study. One dropped out at six weeks because of side-effects, and one was lost to follow-up between weeks six and eight. As both dropouts completed most of the study protocol, their data were analysed as the last result (six week rating) carried forward. The results are summarized in Table 2.

Impulsivity

Impulsivity scores (WSI) showed significant improvement over time: WIS, $p = 0.001$.

Depressed/dysphoric mood

Both subjective (BDI) and objective (HDRS) measures of depressed/dysphoric mood showed significant improvement: BDI, $p = 0.02$; HDRS, $p = 0.03$.

Global psychopathology

Both self-rated (SCL-58) and observer rated (BPRS) measures of global psychopathology showed significant improvement over time: SCL-58, $p = 0.006$; BPRS, $p = 0.01$.

Global functioning

Clinical rated global functioning (GAS) showed significant improvement: $p = 0.004$.

Life stressors

Life stressors (LS-WSI) did not change significantly: LS-WSI, $p = 0.281$.

Side-effects

Tardive dyskinesia (TD)

No signs of TD (as measured by the Abnormal Involuntary Movements Scale) were observed over the course of the study.

Extrapyramidal

Extrapyramidal side-effects were assessed by patient self-report. Of the 13 subjects studied, nine (69%) complained of treatment emergent extrapyramidal symptoms. Of this number, six (66%) were considered minimal or mild, three (33%) moderate, and none severe. The one dropout from side-effects experienced akathisia which was not responsive to procyclidine prophylaxis.

DISCUSSION

Although this is a preliminary open study of a small number of adolescent subjects with BPD and the usual caveats regarding this type of investigation apply to the data presented here, the positive outcome in this group of disturbed and difficult to treat adolescents suggests that a low dose (3 mg per day) of flupenthixol may be an effective and relatively well tolerated short-term pharmacologic treatment. Furthermore, the effects of flupenthixol seem to be global in nature, positively effecting a variety of symptoms including impulsivity, dysphoric mood and general psychological functioning.

Flupenthixol is a neuroleptic of the thioxanthene class which exhibits dopamine (D_1 and D_2 receptor), serotonin ($5\text{-}HT_2$ receptor) and alpha one adrenergic receptor effects. Its antipsychotic activity is thought to be related to its post-synaptic D_2 action which occurs at moderate to high doses (9 mg to 18 mg per day) while its antidepressant activity (occurring at lower doses of 3 mg to 6 mg per day) may be due to either its action on $5\text{-}HT_2$ receptors or its propensity to increase dopamine activity through autoreceptor effects (Hyttel et al 1985; Gawin et al 1989; Robertson and Trimble 1982; Deakin 1989).

The exact mechanism of flupenthixol's potential multiple therapeutic actions in this group of BPD teenagers is not clear. Studies in adult depressives have demonstrated that low dose flupenthixol is as effective an antidepressant as amitriptyline, nortriptyline or fluvoxamine but with fewer side-effects and possibly an accelerated onset of action (Trimble and Robertson 1983; Merskey 1986; Hall and Coleman 1973; Frolund 1974; Ovhed 1976; Tam et al 1982; Young et al 1976; Johnson 1979; Hamilton et al 1989). However, it is unlikely that this antidepressant effect alone led to the improvements noted in our study population because: 1. the symptoms improved across multiple domains; 2. BPD has not been shown to be a depressive equivalent (Gunderson and Phillips 1991); and 3. this study excluded any patient who met DSM-III-R criteria for any current affective disorder.

Flupenthixol is also a potent antipsychotic, albeit at doses higher than those used in this study (Kong and Yeo 1989; Singh 1984; Carney and Sheffield 1976; 1975; 1973; Ehmann et al 1987). However, although some evidence suggests a possible common neurobiologic diathesis in some areas of central nervous system functioning between BPD and schizophrenia (Kutcher et al 1989; Siever et al 1986; Lahmeyer et al 1989), the antipsychotic effects alone of flupenthixol are also insufficient to account for the type of clinical improvement demonstrated in this sample. Thus, the most parsimonious explanation is that a combination of dopaminergic and serotonergic effects acting together may most likely underly the clinical efficacy demonstrated by flupenthixol in this population of BPD teenagers.

Furthermore, although the potential effect of other intervening variables on this sample cannot be excluded given this design, the statistical strength of the changes across all domains studied and the lack of relationship of outcome to ongoing life events measured during the study suggest that the treatment outcome is due primarily to the medication effect of low dose flupenthixol. Additionally, many of the extrapyramidal side-effects reported by the adolescents were generally mild or moderate in severity. Finally, although the time frame of this preliminary investigation was relatively short, no signs of tardive dyskinesia could be identified on repeated clinical examinations. These findings suggest that flupenthixol (in the short-term at least) may be relatively well tolerated in this population.

The findings of this study suggest the following:

1. Low dose flupenthixol may be an effective and well-tolerated medication for use in the short-term management of adolescents with BPD.
2. Short-term therapeutic efficacy of flupenthixol shows a global effect across multiple domains including impulsivity, depressed/dysphoric affect, general psychopathology and global functioning.
3. The therapeutic effects of low dose flupenthixol may arise from a combination of its central nervous system dopamine and serotonergic effects.

Given the significant morbidity associated with this disorder and the potential for improving outcome if effective interventions can be applied in the adolescent years, further investigations into the pharmacologic treatment of adolescent BPD are warranted. Double-blind, placebo-controlled trials which evaluate not only the efficacy of flupenthixol over both short- and long-term periods, but also the social, academic and interpersonal functioning of the patients, in addition to the symptoms of BPD, are especially necessary.

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